Development of a new QSPR based tool to predict explosibility properties of chemical substances within the framework of REACH and GHS

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1. Introduction

The new European regulation of chemicals named REACH (for "Registration, Evaluation and Authorization of Chemicals") turned out in the practical registration phase in December 2008. It requires the new assessment of hazard properties for up to 140000 substances. However, the complete experimental characterization of toxicological, ecotoxicological and physico-chemical hazards is time-consuming, costly, sometimes not feasible at the R&D stage and potentially risky. In this context, the development of alternative predictive methods for assessing hazardous properties of chemical substances is promoted in REACH and in the related new European classification system of substances CLP (Classification, Labelling and Packaging of chemical substances and mixtures).
Upon the available alternative approaches, Quantitative Structure-Property Relationships (QSPR), extensively already used in biological and toxicological applications to reduce unnecessary animal testing, are now also developed to predict physico-chemical properties.
This contribution focuses on models established to predict accurately two physico-chemical properties of potentially explosive nitroaromatic compounds: the heat of decomposition and the electric spark sensitivity. An original approach associating the QSPR method to quantum chemical calculations was developed. Once validated, models are expected to be integrated into a global tool for the estimation of explosibility hazards.

2. Presentation of the tool

Regulatory frameworks consider explosion hazards by characterizing different aspects of the phenomena. Tests to deflagration and detonation estimate if the decomposition can initiate deflagration and, then, propagate to detonation. Explosive power represents the amount of energy released during the explosive decomposition. Sensitivities characterize the ability to react under external solicitation: mechanical (impact or friction sensitivity), thermal (heat sensitivity) or electrostatic (electric spark sensitivity).
Our project aims to develop a tool that gathers and uses predictive models to give a first evaluation of explosibility hazards to complement the experimental assessment process. This tool, presented in figure 1, comprises 4 main modules.

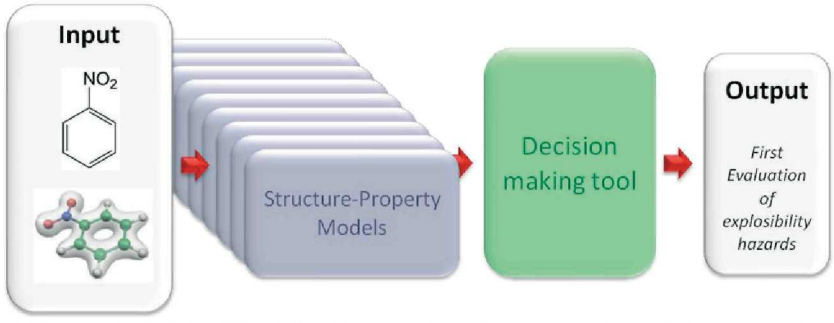

Figure 1: Global tool for the evaluation of explosibility hazards

2.1. Input

The input module collects molecular geometric and electronic structures of the investigated substances and calculates molecular descriptors. In our combined DFT-QSPR approach, models are based on molecular descriptors extracted from density functional theory (DFT) calculated structures, optimized at PBE0/6-31+G(d,p) level in Gaussian03 package [1] and more than 300 molecular descriptors are computed using CodessaPro software [2].

2.2. QSPR models

The QSPR approach consists in correlating quantitatively the experimental property with the previously calculated descriptors.

$$\text{Property} = f(\text{Descriptors}) \quad (1)$$

An experimental data set gives the property measured values. These values have to be obtained within a single protocol and with a high accuracy to ensure the best reliability.
Different kinds of descriptors characterize the molecular geometric and electronic structure:

- Constitutional: number of specific atoms, functional groups, bonds;
- Topological: atomic connectivity giving information about size, branching degree;
- Geometric: distances, angles, molecular volume;
- Quantum chemical: atomic charges, molecular orbital energies, reactivity indices.

Then, the model can be set up using artificial neural networks or genetic algorithms. Here, statistical multilinear regressions were computed in CodessaPro. The fitting of the models was characterized by the correlation coefficient (R^2) and their robustness was estimated using the cross-validation method (R^2_{cv}).

2.3. Decision making tool

Once QSPR models are validated, they can be used within a classification procedure. A decision making tool gathers QSPR calculated properties following the general regulatory guidance. Adequate models are selected upon the studied molecule and the properties to be determined. A key point concerns uncertainties to estimate, not only accuracy but also the need of further experimental characterization.

2.4. Output

To the end, this global tool gives a first evaluation of the possible classification of substances based on calculated properties and indicates whether further experimental characterization is needed or not. It could also help in substitution goals or R&D processes to estimate the explosive properties of new substances before synthesis.

3. Example of QSPR models

3.1. Heat of decomposition

Thermal stability is an important behavior of explosive substances since it gives information about the energy released during decomposition. If experimental characterization is well defined, using calorimetric analyses [3], only few predictive models have been up to now developed. Grewer [4] revealed the influence of some chemical groups on decomposition temperatures. More recently, Saraf et al. [5] simply assumed that the heat of decomposition was proportional to the number of nitro groups in the molecule (n_{NO2}).

In our study [6], the heats of decomposition of 22 nitroaromatic compounds were extracted from literature [7]. The computed multi-linear model reveals highly correlated with experiments (R^2=0.98), as shown on figure 2, and is based on a restricted number of parameters to ensure against any over-parameterization, which would reduce predictivity.

$$-\Delta H\ (kJ/mol) = 401{,}6\ n_N + 2092{,}2\ BO_{N,avg} + 13287\ E_{O,max} - 3148{,}5 \qquad (2)$$

where n_N is the number of nitrogen atoms, $BO_{N,avg}$ the average bond order for a nitrogen atom and $E_{O,max}$ the maximum electrophilic reactivity index for an oxygen atom. These descriptors characterize the number of nitro groups, via n_N, and their ability to leave the molecule, via two local reactivity indices ($BO_{N,avg}$ and $E_{O,max}$). This is consistent with chemical knowledge since heat of decomposition represents the amount of released energy by the loss of nitro groups. So, the model is not only correlated but also chemically consistent.

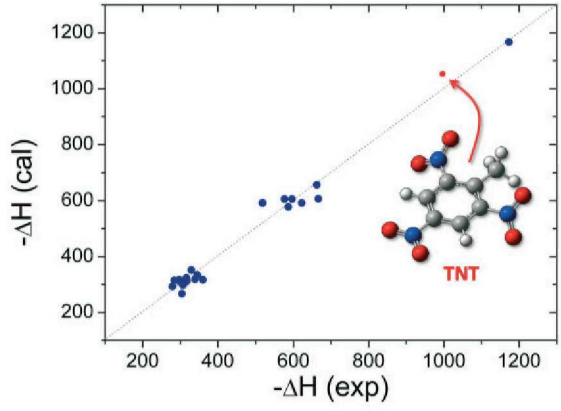

Figure 2: Plot of calculated decomposition enthalpies (in kJ/mol) versus experimental values according to equation (2)

Moreover, the obtained 3-parameter model gives good predictivity for the TNT molecule, out of the initial set of data. To strongly evaluate the predictive power of the model, further external validation is needed, but the small size of our data set (22 molecules) was not sufficient to divide it into training and validation sets. Nevertheless, cross-validation method demonstrated good robustness for this model (R^2_{cv}=0.97).

3.2. Electric spark sensitivity

Concerning electric spark sensitivity (E_{ES}), only few predictive approaches have been proposed so far, due to the complexity of experimental characterization, currently performed with various protocols. Moreover, microscale mechanisms are, up to now, not completely clarified, even if relations were exhibited with the molecular structure, thermal reactivity, mechanic sensitivity or detonation properties [8, 9]. To our knowledge, the only QSPR type approach was proposed by Keshavarz recently for nitroaromatic compounds using constitutional descriptors (R^2=0.77) [10].
Our study was based on a more extended set of descriptors for 26 nitroaromatic compounds. A 4-parameter model was developed [11] with high correlation with experiments (R^2=0.90).

$$E_{ES}(J) = 29.6\ n_{single} + 63.3\ N_{C,max} + 168.4\ Q_{C,min} - 27.8\ V_{C,min} + 99.4 \qquad (4)$$

where n_{single} is the relative number of single bonds and $N_{C,max}$, $Q_{C,min}$ and $V_{C,min}$ are the maximum nucleophilic reactivity index, the minimum charge and valence for a carbon atom, that can be related to the C-NO_2 bond. Beside, general assumption considers the loss of

nitro group as the rate limiting step of decomposition in nitro compounds. So, this new model is chemically consistent. Improvement is expected by enlarging the data set, making external validation possible, but its current performances look yet better than Keshavarz one (R^2=0.90 vs. 0.77), as shown in figure 3.

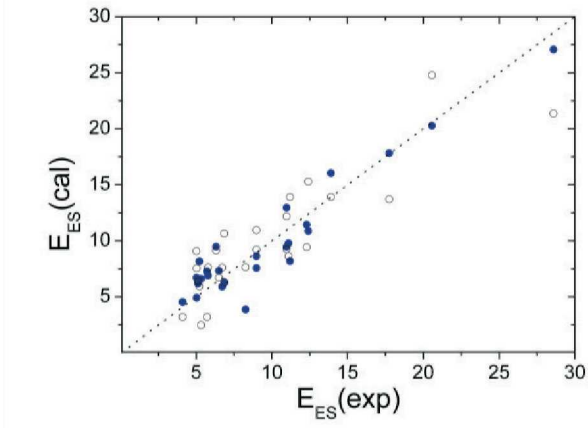

Figure 3: Plot of calculated electric spark sensitivity (in J) versus experimental values according to equation 4 (in plain circles) and Keshavarz's model [10] (in wide circles).

4. Conclusion

Two physico-chemical properties related to the explosibility of nitroaromatic compounds have been investigated using a combined DFT-QSPR approach: the heat of decomposition and the electric spark sensitivity. The developed models need consolidations to validate their predictivity using extended data sets, but they already upgrade the existing models with correlations up to R^2=0.98 and 0.90. Moreover, they integrate chemically consistent descriptors related to the C-NO_2 bond, the critical reactive site for the decomposition of nitroaromatic compounds [12, 13].
Once strongly validated models are obtained, they will be associated within a global tool to assess explosive hazards in the line of the search of new methods (required by REACH), not replacing but complementary to experimental tests, to provide first evaluation of hazards and to guide to further experimental investigation when necessary.

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